c release, caspase activation and apoptosis in Bid-deficient hepatocytes. All the above evidence suggests that ROS may play an important role in regulation of Bax translocation and the subsequent mitochondrial dysfunction and apoptosis even in the absence of Bid in hepatocytes.

346 STEROID HORMONE INDUCED CELL SURVIVAL RESPONSE IN CARDIOMYOCYTES

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Steroid hormones regulate many physiological and cellular processes after binding to nuclear receptors. Psychological stress is known to induce an elevation of corticosteroids in the circulating system. Although corticosteroids induce apoptosis in lymphocytes and neuronal cells, we found that in cardiomyocytes pretreatment of corticosterone (CT) prevents apoptosis induced by doxorubicin and several other toxins. Progesterone (PG), aldosterone and retinoic acid, but not estrogen, testosterone, androstenedione or phenobarbitale, also elicit a cell survival response. Mifepristone, an antagonist of glucocorticoid receptor and progesterone receptor, abolishes the cytoprotective effect of CT and PG. CT appears to activate cell survival signaling pathways, i.e. phosphoinositide 3-kinase (PI3K) and Akt, in a glucocorticoid receptor dependent manner. Microarray analyses reveal that CT or PG causes increases in the expression over 100 genes, among which are bcl-xL and a number of genes encoding detoxification enzymes and antioxidant or metal binding proteins. The antiapoptotic effect of CT is mediated in part by bcl-xL expression as demonstrated by siRNA experiments. While CT regulates bcl-xL gene at the transcriptional level, PG appears to increase the stability of bcl-xl RNA. PG but not CT induces the expression of NAD(P)H: Quinone Oxidoreductase 1 (NQO1) via a Nrf-2 independent mechanism. Although activating NQO1 with β-naphthoflavone induced a small degree of cytoprotection, inhibiting NQO1 with dicumarol failed to abolish PG induced cytoprotection. Our studies suggest that steroid induced cell survival is a complex response that may involve several pathways including PI3K activation, increased expression of prosurvival factors of bcl-2 family, and increased expression of antioxidant/detoxification genes.

347 ADVANCES IN ASBESTOS TOXICOLOGY AND EXPOSURE ASSESSMENT

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Occurrences of asbestos-related contamination, such as the vermiculite mine in Libby, Montana, and the World Trade Center, have highlighted the need to update the state of science with regard to asbestos toxicity and exposure assessment. The purpose of this workshop is not only to provide an overview for toxicologists, but also to highlight the advances in a number of important areas. Recent work by US EPA in examining the carcinogenic and non-carcinogenic effects of asbestos will be presented. The technical issues of assessing asbestos hazard in an indoor environment are presented. New data from NIOSH will update the dose-response analysis of the mortality of textile workers. Research into cellular and molecular mechanisms of lung and pleural diseases is opening up new hypotheses on the mechanisms of action of asbestos toxicity. In the area of asbestos exposure assessment, improvements in analytical and counting methodologies will be discussed. This presentation will also provide some preliminary results of a sensitivity analysis being conducted by EPA on a quantitative cancer model that divides asbestos fibers into four bins (diameter < .4um), as a function of mineral type (chrysotile versus amphiboles), and length (5-10um, > 10 um). EPA has been working to establish quantitative uncertainty bounds around the fitted model parameter estimates and performing sensitivity analyses to help characterize confidence in these values. The preliminary results for lung cancer indicate that confidence in the fitted parameters shows that the best results are obtained for the potency values for the long fibers, as compared to the potency values for shorter fibers.

348 ASBESTOS NONCANCER EFFECTS - INTEGRATED RISK INFORMATION SYSTEM (IRIS)UPDATE

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The non-cancer assessment and the cancer assessment on asbestos contained in EPA's Integrated Risk Information System (IRIS) database dates back to 1986. The Agency is developing a health assessment of noncancer effects of asbestos exposure to support the IRIS file as a background document. This assessment includes current information on the toxicity and risk for the non-cancer effects associated with asbestos exposures using information from the published scientific literature. The assessment indicates that amphiboles may be more toxic than serpentine. On the other hand, there is paucity of data for fiber shape and size for non-carcinogenic endpoints. Description of different health effects includes clinical correlation of radiologic findings, reduction in pulmonary function, and clinical signs and symptoms. The occurrence of noncancer disease entities such as pleural effusion, pleural plaques/fibrosis, atelectasis, and asbestosis is evaluated. Preliminary evaluation suggests that pleural plaques are the calling card of asbestos exposure. Though pleural effusion and pleural fibrosis are found to be associated with environmental exposure to asbestos they are not exclusively due to asbestos exposure. There is paucity of data on atelectasis and asbestosis due to environmental exposure. The possibility of the immunotoxicity, reproductive/developmental toxicity and other nonpulmonary effects in humans is being explored but the literature on these effects is extremely limited. Of the various aforementioned noncancer effects, a critical effect needs to be identified for the quantitative toxicity assessment. The pleural plaques constitute the most robust and defensible critical effect to base the safety and modifying factors. Once the non-cancer assessment is final, the Agency will proceed with its reassessment of the cancer effects associated with asbestos.

349 FIBER SIZE-SPECIFIC EXPOSURE ESTIMATES AND UPDATED MORTALITY ANALYSIS OF CHRYSOTILE ASBESTOS TEXTILE WORKERS

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Sponsor: L. Hofmann.

Previous epidemiological studies of asbestos exposure and lung disease have estimated airborne exposures using the number of fibers >5 μm/cm^3 (length/width ratio of at least 3). However, evidence from toxicological studies suggests that the longer fibers may be more biologically significant than the shorter fibers. To formally assess this question, NIOSH has re-analyzed the original asbestos samples for a South Carolina textile worker cohort (Dement et al. 1983; Am J Ind Med 4:399-433) using transmission electron microscopy to obtain the bivariate (diameter and length) fiber size distributions. These data were used to develop a new bivariate job-exposure matrix for the textile workers, in which the previous phase contrast microscopy-based exposure estimates, by department and job, were adjusted to account for fiber dimension. These fiber size-specific exposure estimates include diameters from <0.3 μm to >3 μm and lengths from <1.5 μm to >40 μm. The differences in these fiber dimensions across departments were as much as five-fold. In addition, NIOSH has updated the mortality follow-up for this cohort, which includes an additional 701 deaths and a total of 118,474 person-years at risk. This analysis confirmed the findings of a previous analysis (Stayner et al. 1997; Occup Environ Med 54(9):646 52), which showed statistically significant exposure-response relationships between cumulative exposure to chrysotile fibers >5 μm/cm^3 and lung cancer or asbestosis. Analyses are underway to determine the influence of fiber dimension on lung disease risk. These findings will be useful in quantitative risk assessment, as well as in determining the concordance of epidemiological and toxicological studies and in evaluating the scientific evidence for a fiber size-specific risk assessment paradigm.

350 MECHANISMS OF FIBER CARCINOGENESIS: FROM MITOCHONDRIAL DAMAGE TO SILENCING OF THE BIGH3 GENE

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Sponsor: E. Hofmann.

Asbestos is an important environmental hazard in the U.S. and remains the primary occupational concern in many developing countries. Although asbestos is carcinogenic and induces both bronchogenic carcinomas and pleura and peritoneal mesotheliomas in humans, the underlying mechanisms of fiber carcinogenesis are not known. For decades, asbestos has been considered a non-genotoxic carcinogen. Using mutagenic assay system that is efficient in detecting multilocus deletions, we showed previously that chrysotile is indeed a potent gene and chromosomal mutagen. Furthermore, phagocytosis of asbestos by target cells and the resultant oxyradical production are important mechanistic factors in fiber mutagenesis. To demonstrate that extranuclear target may play a functional role in mediating fiber mutagenesis, enucleated cytoplasts were shown to induce oxyradicals in response to fiber treatment. Furthermore, fiber-treated cytoplasts, upon fusion with non-treated karyoplasts showed a three-fold increase in 8-hydroxyl-deoxyguanosine, a biomarker for oxidative DNA damage. Using an immortalized human bronchial cell model, we have shown that chrysotile fibers induce step-wise neoplastic transformation of these cells that form progressive growing tumors when inoculated into

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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